

**TREATMENT OF DIABETES MELLITUS AND
INSULIN RECEPTOR SIGNAL TRANSDUCTION**

5	<u>TABLE OF CONTENTS</u>	<u>Page</u>
	1. INTRODUCTION	1
10	2. BACKGROUND OF THE INVENTION	1
	2.1. SIGNAL TRANSDUCTION	1
	2.2. THE INSULIN RECEPTOR	4
	2.3. DIABETES MELLITUS	5
15	3. SUMMARY OF THE INVENTION	7
	4. BRIEF DESCRIPTION OF THE FIGURES	8
	5. DETAILED DESCRIPTION OF THE INVENTION	11
20	5.1. MODULATION OF PTPs THAT REGULATE IR SIG- NAL TRANSDUCTION	12
	5.1.1. USE OF COMPOUNDS THAT MODULATE THE IR PTP	14
	5.1.2. RPTP ANTIBODIES	14
25	5.1.3. GENE THERAPY	16
	5.1.4. ANTISENSE AND RIBOZYME APPROACHES .	17
	5.1.5. PHARMACEUTICAL FORMULATIONS AND MODES OF ADMINISTRATION	19
	5.2. ASSAY SYSTEMS FOR DRUG SCREENING	23
30	5.2.1. COEXPRESSION OF RPTPS AND IR-PTK AND GENERATION OF ENGINEERED CELL LINES .	25
	5.2.2. SCREENING ASSAYS	32

 0940580-03404
 TOCTED-08507860

		<u>Page</u>
	6. EXAMPLE: TRANSIENT COEXPRESSION OF THE INSULIN RECEPTOR AND PTP	41
	6.1. MATERIAL AND METHODS	41
5	6.2. RESULTS	42
	7. EXAMPLE: DEMONSTRATION OF AN <i>IN VIVO</i> SELEC- TION SYSTEM FOR INSULIN RECEPTOR ACTIVATION .	44
	7.1. MATERIALS AND METHODS	44
10	7.2. SELECTION AND ANALYSIS OF CELLS BY TRANSFECTION WITH cDNAS ENCODING PTPS . .	45
	7.2.1. INSULIN-INDUCED CHANGE IN PHENOTYPE	45
15	7.2.2. AUTOPHOSPHORYLATION ASSAY BY WESTERN BLOT	46
	8. Example: Direct interaction between IR and RPTP α	47
	8.1. Materials and Methods	47
20	8.2. Coimmunoprecipitation of RPTP α with IR .	48
	8.3. Demonstration of elution of RPTP α from autophosphorylated IR	49
25	9. Example: Screening Assay for Inhibitors of Insulin Receptor-Related Phosphatase Activity	51

30

35